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Summary

- Imaging contrast agents, administered intravenously, are diverse, can be used for diagnostic and therapeutic purposes, and have specific regulatory requirements and development considerations.

- Collaborative relationships between industry and academia may provide the best approach for the development of these agents.

- Additional opportunities for development and commercialization include software specific for the analysis of contrast-enhanced examinations.

- There are special considerations for each class of imaging contrast agents with regards to market growth and potential avenues for future development.

Development of Radiographic Contrast Agents for Diagnostic Imaging

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Topic Relevance by Timeline

Summary

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- Collaborative relationships between industry and academia may provide the best approach for the development of these agents.
- Additional opportunities for development and commercialization include software specific for the analysis of contrast-enhanced examinations.
- There are special considerations for each class of imaging contrast agents with regards to market growth and potential avenues for future development.

Introduction

Contrast agents for diagnostic imaging—including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and nuclear medicine/positron emission tomography (NM/PET)—are crucial for clinical diagnosis, monitoring of treatment response, and functional evaluation. According to projections, the global market for biologic imaging agents is estimated to grow 10.6% (from $14.4 billion to $23.9 billion) between 2017 and 2022 (Agdeppa and Spilker).

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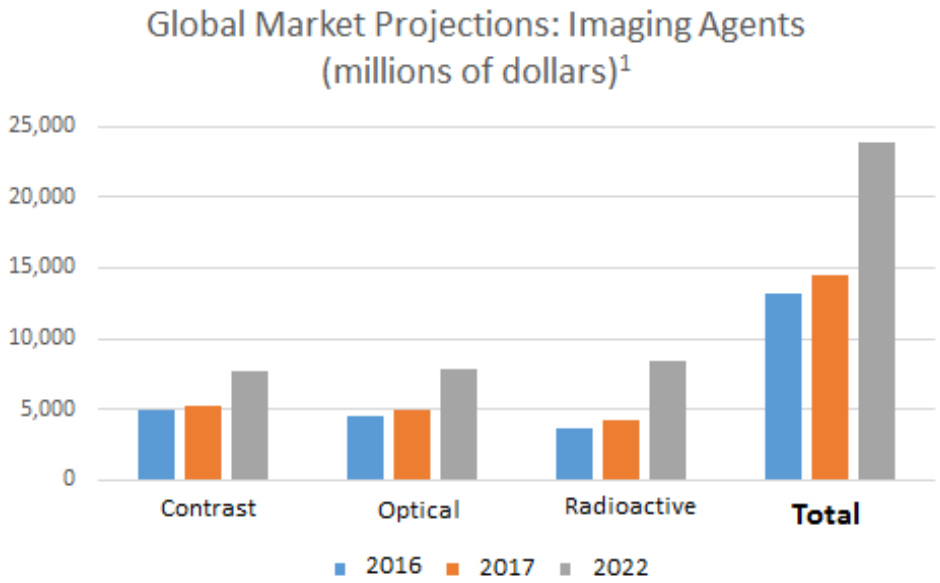
Therefore, to capitalize on this growing market, an understanding of the specific processes for the development and commercialization of these products is warranted.

Figure 1. Global Market Projections of Imaging Agents.



Legend: Blue bars signify agents in the year 2016. Orange bars signify agents in the year 2017. Gray bars signify predictions of agents in 2022.

Interests of Potential Developers

Potential developers include members of the industry, academia, and collaborative partnerships between the two entities. Diagnostic imaging agents are generally less toxic than interventional drugs and many are widely used, thus saturating the existing market and deterring investigators from exploring new agents and approaches. Despite the large quantities of imaging agents administered clinically, the relatively low reimbursement rates contribute to low profit margins, which generally deters industry partners from exploring this category of drug development. Notable exceptions exist, however, such as the recent acquisition of an amyloid PET radiotracer company for nearly $300 million, with an additional $500 million based on regulatory/commercial milestones, by Eli Lilly & Company, a global pharmaceutical company. Furthermore, when utilized for therapeutic or interventional indications, the large initial investment is offset by the high financial reward, which is appealing to these companies. Academic interests include novel imaging approaches and improving the diagnosis and treatment of patients, but the costs associated with Phase 1 and Phase 2 clinical trials create a barrier for clinical translation in the academic setting (Joshi). Therefore, collaborative partnerships between academia and pharmaceutical companies may offer the best opportunity to mitigate these barriers in development and maximize potential benefits (see the chapter “Forming and Maintaining Meaningful Partnerships Between

Academic Scientists and Corporations"). One such method of collaboration that appeals to the interests of both industry and academia is "theranostics" where the contrast agent is used both for diagnosis and either therapy or guiding intervention to allow the personalized treatment of patients. There has been a growing interest on the part of the National Institutes of Health (NIH) to fund this type of research. For example, theranostic nanomedicine is a specific subsection within the NIBIB, and theranostics is now listed as the "highest priority challenge topic" for NIAMS.

Development in the United States

Many available imaging contrast agents for CT and MRI are long established and widely used. Emerging agents have also recently been introduced in the United States, particularly in the realm of US and NM/PET imaging. This juxtaposition of different classes of imaging agents highlights the complexity associated with the expansion and development of imaging contrast agents, which hinges upon either the improvement of existing agents or the development of novel imaging drugs. The Food and Drug Administration (FDA) provides guidance in this process (Office of the Commissioner; Center for Drug Evaluation and Research, "Developing Medical Imaging Drug and Biological Products Part 1: Conduc"). To summarize their provided materials, if a contrast agent is currently approved, it can be approved for use with a class of devices (e.g., CT, MRI, US) (Table 1), but if the specific contrast agent requires certain software for interpretation, it may require approval as a combination product, and the FDA Office of Combination Products can serve as a valuable resource. Imaging software has traditionally been approved independently of contrast media and often as a component of imaging systems. However, the continued growth of imaging agents for NM/PET, which may require specialized software packages for analysis and interpretation, may necessitate classification as combination products.

Non-Radiolabeled Agents

For non-radiolabeled agents, 501(k) submissions are required for adding approved contrast agents to a device, or for a new indication; if the proposed use is different from current labeling, New Drug Application (NDA) supplements are required (see the chapter "FDA Device Regulation: 510(k), PMA"). These processes are complicated by the fact that imaging contrast agents are often approved only for essential indications but frequently are clinically used "off-label," particularly in children and for MRI (Hung).

Table 1. Quantification of Agents Based on Type and Modality.

Modality	Type of Agent	Number of Agents Currently Approved in United States
Computed Tomography (CT)/Fluoroscopy (XA)	Iodine-based	6
Magnetic Resonance Imaging (MRI)	Gadolinium-based	7
Ultrasound (US)	Lipid Microbubble	3
Positron Emission Tomography (PET)/ Single-Photon Emission Computed Tomography (SPECT)	Radiolabeled	≥10

Development of novel non-radiolabeled contrast-based media requires extensive safety data and confirmation. Approval requirements include a clinical safety assessment, which provides preclinical data on dose and volume, the effects of drug accumulation, and underlying properties. In this process, non-radiolabeled contrast agents can almost always be classified as "therapeutic agents" in FDA materials, as a large dose is required for adequate administration. As these agents are typically used in high doses at a limited number of single-dose administrations, long-term use repeat-dose safety trials are generally not required for approval. The contrast agent should demonstrate added benefit to one of the following specific categories: structure delineation, disease/pathology detection or assessment, function, physiologic or biochemical assessment, diagnostic or therapeutic patient management, or multiple indications. While this seems straightforward, there are special requirements for combination products, and guidance from the FDA Office of Combination Products is particularly important during this process (301-427-1934; combination@fda.gov; www.fda.gov/CombinationProducts/default.htm).

Radiolabeled Agents

Radiolabeled imaging contrast agents, used for NM/PET indications, have a more complicated developmental pathway as they are composed of more diverse chemical compounds and contain radioactive materials. PET-specific agents will be briefly discussed here to illustrate differences from non-radiolabeled agents (Josephson and Rudin). For one, the FDA requires an NDA or an Abbreviated New Drug Application (ANDA) for all PET drugs. As doses administered are typically in the microdose range, extensive pharmacology and toxicology safety information is often not necessary, and the FDA encourages pooling of existing data from multiple sources. Particularly for radioactive agents used for research, depending on the intent of the research (clinical trial

versus basic science), Investigational New Drug (IND) approvals may be needed. The use of microdose agents may also allow more expedited approaches for early-stage research, including filing an Exploratory IND (eIND) application and going through the Radioactive Drug Research Committee (RDRC), which is handled through a local institutional RDRC, whose action is reviewed and monitored by the FDA. Some agents may be considered medical devices—for example, Yttrium-90-labeled microspheres for liver tumor treatment—and may be eligible for an Investigational Device Exemption (IDE).

Lastly, reimbursement potential from insurance companies and from the Center for Medicare and Medicaid Services (CMS) should be considered during the development process, as this information may inform investment decisions and research processes. Imaging contrast agents typically are billed as drugs required for an imaging study (typically CT and MRI) or as an add-on charge to a clinically indicated examination (US contrast agents). NM/PET agents usually fall into the former category but may also be billed as specific treatment procedures for radionuclide therapy. Currently, a specific mechanism exists through CMS—the coverage with evidence development—to demonstrate the impact and medical utility of an FDA-approved agent to assure insurance coverage while conducting a clinical research study and to encourage future coverage by all insurers. Once such example is the "Imaging Dementia—Evidence for Amyloid Scanning" (IDEAS) study, which obtained CMS coverage for amyloid PET examinations while investigating the medical necessity and patient benefits. Ultimately, especially in light of ongoing changes to regulatory and reimbursement requirements, discussion with the FDA and possibly the CMS early in the developmental process may be worthwhile.

Intellectual Property

As discussed previously, the generally low financial yield with contrast agent development encourages developers to more closely guard their intellectual property (see the chapters "Intellectual Property: Ownership and Protection in a University Setting" and "Intellectual Property: Commercializing in a University Setting"). However, this approach can still be cost-prohibitive for licensors of niche imaging contrast agents with a small market size. Therefore, partnerships between academia and the industry should be considered, as complementary expertise and infrastructure can be mutually beneficial in drug development by allowing the merging of resources, including intellectual property. For example, the pooling of patents under one primary sponsor/institution streamlines regulatory processes and provides greater flexibility in development. Collaboration between pharmaceutical and imaging companies also improves the cost-effectiveness of drug development by allowing the coupling of therapeutics with molecular imaging (Kohli et al.). This approach streamlines the potential development of targeted therapy, as exemplified by novel Alzheimer's imaging agents, where the clinical benefit lies with coupled treatment agents rather than solely with diagnosis. Lastly, collaboration with industry partners and the sharing of intellectual property allows coordination of multi-institutional investigations, which can increase patient access, subject accrual, and breadth of experience in different clinical settings,

which ultimately can accelerate drug development and regulatory approval. In recognition of these beneficial relationships, specific funding mechanisms for academic-industrial partnerships exist through various NIH institutes, such as the National Center for Advancing Translational Sciences (NCATs).

Patents

Development of imaging contrast agents is typically under broad existing patents specific to the type of agent. For example, current patents for "contrast agent and its use for imaging" (WO2014041150A1), "contrast agents for diagnostic imaging" (WO1995028179A1), and "contrast agents and methods for preparing contrast agents" (US8173105B2) have been granted. This approach is different for molecular imaging agents, for which patents are specific to the type and structure of the molecule. These patents include "labeled molecular imaging agents, methods of making and methods of use" (US20100272641A1), "molecular imaging agents" (US20110293519A1), and "molecular imaging contrast agents and uses thereof" (WO2015134671A1). Innovative development of imaging contrast agents will require either a new patent or licensing under previously established patents. Evaluating the current patents and the breadth of coverage will inform this process.

Software Development

One unique characteristic of some imaging contrast agents is the potential for development of specific software for analysis and interpretation of imaging studies (Lusic and Grinstaff). For example, as development and use of ultrasound contrast agents (UCAs) have expanded in the United States, clinical need for quantitative analysis of UCA kinetics for perfusion assessment has prompted the exploration of specific software packages. Some products that perform time-intensity curve analysis have been developed and licensed by vendors, integrated into the US system, and marketed as add-on purchases to institutions (i.e., QLAB, and Philips Healthcare North America). Others are stand-alone software packages that are compatible with many different US systems, such as VueBox® (Bracco Diagnostics) and SonoLiver® (TomTec Imaging Systems). Development and use of these technologies may require material transfer agreements (MTAs).

As a corollary to independent software development, many vendors have innovation arms that sponsor partnerships with developers, typically in the form of venture capital. However, in addition to financial investment and commercialization resources, these relationships provide developers with access to global infrastructure and networks. Engaging in these partnerships offers multiple opportunities for growth and development of software technology. Ultimately, collaborative efforts with industry and manufacturing partners throughout the process may be beneficial to both parties.

Additional factors related to imaging datasets and analysis, including data storage and protection and computer learning algorithms (artificial intelligence), are worth mentioning, as they warrant attention from software developers and vendors and provide another unique market opportunity for potential commercialization. However, these topics are expansive, apply broadly to all imaging studies regardless of contrast administration, and are outside the scope of this review. Current relevant literature covers these issues in greater detail (Mayo et al.; Maier and Schreiber).

Special Considerations by Agent Class

Iodine-based contrast agents

CT and fluoroscopic angiography—widely used imaging technologies—require the use of iodine-based contrast agents for diagnosis and interventional guidance (Moek et al.). These agents are also used as enteric contrast agents for fluoroscopy and CT, however, despite higher profit margins in this capacity, there has been a loss of market share due to decreased use. The market is dominated by a few reliable agents, with limited growth for comparable agents. However, these agents are limited by their renal excretion and relative contraindication in patients with kidney problems such as renal insufficiency or dialysis requirements. Therefore, there is a current void in the market for contrast agents that avoid renal toxicity, which offers a potential target for future developers (Pierre et al.).

Gadolinium-based contrast agents (GBCAs) for Magnetic Resonance Imaging

The MRI contrast agents most commonly utilized clinically are composed of gadolinium polymers. These contrast agents are crucial for many imaging indications including identification and visualization of neoplasm and metastatic disease, degenerative disease, infection and inflammation, stroke, and musculoskeletal imaging. There are currently 11 FDA-approved GBCAs for MRI, and the current market growth has focused upon the expansion of indications of current agents (Center for Drug Evaluation and Research, “New Warnings for Gadolinium-Based Contrast Agents (GBCAs) for MRI”). In addition to the concerns of nephrogenic systemic fibrosis, rarely seen after administration of gadolinium-based agents in patients with renal disease, theoretical concerns regarding gadolinium deposition, seen primarily with microcyclic agents with repeated administration, have dominated the scientific discourse. This theoretical concern has culminated in the recent safety announcement from the FDA alerting patients to the potential for gadolinium retention with these agents (Center for Drug Evaluation and Research, “New Warnings for Gadolinium-Based Contrast Agents (GBCAs) for MRI”). Therefore, there is great potential for the development of additional agents, such as macrocyclic agents and those not renally excreted, that would avoid these risks.

Superparamagnetic Iron Oxide (SPIO) contrast agents for Magnetic Resonance Imaging

SPIOs are within an emerging class of imaging contrast agents; one SPIO particle formulation has obtained clinical approval in the United States for imaging (Feridex IV®, Berlex Laboratories), while a second SPIO formulation has been approved by the FDA for the treatment of iron-deficiency anemia but is being investigated as an imaging agent in the research setting (Feraheme®, AMAG Pharmaceuticals) (Reimer and Vosshenrich). Several additional SPIO agents are available in foreign countries and under development. These contrast agents undergo phagocytosis after intravenous administration, and the iron components are ultimately incorporated into the normal iron pool of the body and have no risk of nephrogenic systemic fibrosis (Spampinato et al.; Wáng and Idée), thus avoiding some concerns with GBCAs outlined above. Despite these potential comparative benefits, development of SPIO agents has been hampered by the relatively higher rates of hypersensitivity reactions and the decreased sensitivity in evaluating the disease process when compared to GBCAs. Therefore, even though SPIO agents are a promising category for imaging agent development, further dosing and safety data are warranted with both current and future agents. While the development cost is high, the anticipated market volume for these agents is small, thus limiting interest from pharmaceutical companies. Lastly, for those SPIO agents without current approval for imaging, one should consider the concerns regarding lack of insurance reimbursement.

Microbubble contrast agents for contrast-enhanced ultrasound

Ultrasound contrast agents (UCAs) are relatively new in the US market and have shown benefit in diagnostic imaging. With an excellent safety profile and use with US, a noninvasive radiation-free imaging modality, UCAs have been gaining traction in clinical practice. Available FDA-approved diagnostic imaging agents include Optison® (GE Healthcare), Sonovue®/Lumason® (Bracco Diagnostics), and Definity® (Lantheus Medical Imaging). While rare immune-mediated sensitivity reactions have been reported, general safety has been established. Targets for development include exploring methods of quantification and functional imaging and the delivery of therapeutic agents.

Radiolabeled agents for Positron Emission Technology (PET) or Single-Photon Emission Computed Tomography (SPECT)

Imaging contrast agents used in nuclear medicine, including PET or SPECT, are utilized for cancer diagnosis, treatment monitoring, endocrine disorders, and cardiology applications. Relatively new indications include the diagnosis and assessment of neurologic disorders. Commonly utilized agents include fluorodeoxyglucose or FDG (glucose metabolism and disease detection/monitoring), Iodine-123 and Iodine-131 (thyroid disease detection/treatment), Technetium-99m-Sestamibi (myocardial perfusion), and Ioflupane-123 (DaTSCAN for detection of Parkinson's Disease). The impetus for growth in this group is for new disease-specific agents and/or agents focused on specific biologic processes such as neurodegeneration. As these contrast

agents are developed for the targeted detection of disease, and often have a more facile translation pathway, there is a huge potential for relatively easy translation to therapeutic agents. This includes theranostics, where radiolabeled compounds, including small molecules, peptides, and antibodies, may diagnose and treat a disease simultaneously (Wang).

Pediatric Considerations

As briefly discussed above, imaging contrast agents are not always evaluated in children and subsequently they are not specifically approved for use in pediatric patients. In many situations these contrast agents are instead used "off-label" as this is considered the standard of care. This practice, while beneficial clinically, introduces challenges for researchers and developers in investigating the safety and efficacy of these agents in children. Furthermore, research ethicists and institutional review boards consider children a special population by virtue of their inability to provide informed consent. This appropriate classification imparts additional protections upon children, as well as increased regulations and requirements in regards to research methods and processes. Therefore, industry partners are generally reluctant to pursue FDA approval for imaging contrast agents in children. In turn, there is less market competition, which offers ample opportunities for growth and development of contrast agents approved for use in pediatric patients for those companies and institutions willing to investigate this further. Again, collaborative partnerships between industry and academia can help mitigate some of these concerns to allow maximal benefit for pediatric patients, investigators, and developers (see the chapter "Forming and Maintaining Meaningful Partnerships Between Academic Scientists and Corporations").

Obtaining Expert Advice

Development of imaging contrast agents may require the help and guidance of the FDA, as discussed, as well as institutional technology transfer offices (see the chapter "Working with the University Technology Transfer Office"). These resources should be contacted and included early in the process to ensure appropriate development. As imaging contrast agent development is best suited for industry-academia collaboration, industry contacts with device manufacturers may prove beneficial. Discussion with the technology transfer office can be crucial in this process, especially as an academic faculty member is considering presenting results at scientific conferences (which may invalidate future patents if not handled properly). Furthermore, conflict of interest may limit future work by the academic faculty member, and disclosure of information with an industry partner may provide them with a competitive advantage if not properly covered by a nondisclosure agreement (NDA).

Conclusion

Intravenous contrast agents for diagnostic imaging are a large and growing market in the United States, with vast opportunities for developers. Success in development and commercialization will likely depend on collaborative relationships between industry and academia, with consideration of the special circumstances related to these agents described in this chapter.

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